Clinicopathologic Features of Hepatobiliary Tuberculosis: A Ten-year Retrospective Autopsy Series

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Significance: Hepatic tuberculosis is an uncommon and arriving at the diagnosis is often challenging. To shed light on the matter, this study aims to present the clinical and histopathologic findings of hepatobiliary tuberculosis encountered in the autopsy cases.

Methodology: A Retrospective chart review of all autopsies performed in PGH from 2003 up to 2012 was done. All diagnosed cases of hepatobiliary tuberculosis (HBTB) were included and the following were described: chief complaint, cause of mortality, liver function, imaging and histopathology findings.

Results: Out of the 755 autopsies performed, 20 cases included. Mean age was 32-years-old, with a male to female ratio of 1.1:1. Most cases were in miliary form, only 3 cases were localized. Most common chief complaint was decreased sensorium and most common cause of death were acute respiratory failure and TB meningitis. AST, ALT, ALP, bilirubin were elevated, and albumin was low. Ultrasound findings ranged from normal to hepatomegaly, liver mass and biliary ectasia. Macroscopic findings most commonly revealed micronodules. Microscopic findings universally presented with chronic granulomatous inflammation with caseation necrosis and Langhan's type of Giant cells.

Conclusion: Presenting symptoms of HBTB may be unrelated to the gastrointestinal tract. Liver function test derangement are common; however are nondiagnostic. Ultrasound findings may range from normal to a complex mass causing biliary ectasia. Histopathologic findings of chronic granulomatous inflammation with caseation necrosis and Langhan's type of Giant cells are diagnostic; however acquisition of tissue sample is problematic. Therefore, diagnoses and management require a high index of suspicion.

Keyword: Hepatobiliary tuberculosis, autopsy series

I. Introduction

Tuberculosis remains to be one of the most challenging disease entities encountered by physicians to date. It is the sixth leading cause of morbidity and mortality locally; and our country is the ninth out of the 22 highest TB burden countries in the world[1]. In the WHO Global report last 2015, 417 per 100000 Filipinos are afflicted with tuberculosis[2]. Most commonly, tuberculosis manifest as an insidious respiratory infection. However, it can affect other organs and thus manifest in myriad ways.

Hepatic tuberculosis is an uncommon manifestation and can occur either as part of a disseminated process or as a localized hepatobiliary entity. The latter was reported to be more common among Asians, especially Filipinos. There is no explanation for this predilection but it has been suggested that Filipinos may have racial vulnerability to the tubercle bacilli[3]. The clinical presentation of hepatobiliary tuberculosis is very diverse. It can range from being asymptomatic to having mild non-specific symptoms of fever and abdominal pain up to full blown hepatic failure. Laboratory abnormalities are commonly encountered but are non-diagnostic. Imaging examination findings are also non-descript; such as hepato-splenomegaly, hepatic mass in the liver or hilum or findings of biliary strictures. These findings can also be found in other diseases that affect the liver. Hepatic calcifications may support the diagnosis of tuberculosis but are not always present. Diagnosis mainly rely on documentation of the bacilli in biopsy specimen or the classic histo-pathologic findings that support tuberculosis. But often times there are technical difficulties precluding successful specimen acquisition. As such, many physicians still rely on empiric treatment of hepatobiliary tuberculosis in clinical practice

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Given the rarity of the disease, its non specific presentation and findings, and the difficulties encountered when obtaining tissue diagnosis, arriving at the diagnosis is often challenging. A high index of suspicion is required in order to prevent a delay in management of a disease that is curable medically. To shed light on the matter, this study aims to present the clinical and histopathologic findings of hepatobiliary tuberculosis encountered in the autopsy cases performed in the Philippine General Hospital from 2003 to 2012.

Objective:

1. Describe the clinico-pathologic features of hepatobiliary tuberculosis diagnosed from the autopsy cases performed from 2006 to 2015 in the Philippine General Hospital
    a. Determine the prevalence of hepatobiliary tuberculosis
    b. Describe the clinical presentation of the hepatobiliary tuberculosis
    c. Describe the histopathologic findings of hepatobiliary tuberculosis

II. Review of Related Literature

Hepatobiliary tuberculosis

Hepatobiliary tuberculosis involves infection of the liver with *Mycobacterium tuberculosis*. It predominantly occurs in 30-50-year-old age group with a 2:1 male preponderance[4][5]. It presents in three different forms. The most common form is the diffuse hepatic involvement seen with pulmonary infection, or miliary tuberculosis, in 50-80%. Despite the diffuse involvement of the liver, it usually has no sign or symptoms relevant to the liver. The second form is a diffuse hepatic infiltration without recognizable pulmonary involvement, also known as granulomatous or tuberculous hepatitis. These patients present with fever, mild jaundice with or without hepatomegaly. The third and much rare form is the focal/ local tuberculoma, also known as localized tuberculosis. These include solitary or multiple nodules, tuberculoma and tuberculous hepatic abscess without bile duct involvement or bile duct involvement causing obstructive jaundice either by enlarged nodes surrounding the bile ducts or actual tuberculous process in the ductal epithelium producing inflammatory strictures[6][7][8].

Routes of infection involve traversing the hepatic artery from a tuberculous infection of the lungs resulting in miliary tuberculosis, transmission via the portal vein especially if there is a concomitant involvement of the gastrointestinal tract, or by lymphatic spread or due to rupture of a tuberculous lymph node in the portal tract[9].

In the miliary form of hepatobiliary TB, the predominant clinical manifestations are those of the extrahepatic disease. In symptomatic hepatobiliary cases, fever and abdominal pain are the most common symptoms. Jaundice is an uncommon presentation, being present less than one third of patients. Hepatomegaly is the most common physical examination finding. The liver is hard and nodular in about half the cases simulating cancer of the liver, and tender in some cases simulating a liver abscess. Splenomegaly and concomitant tuberculous peritonitis can also be present [10][11][12].

Biochemical abnormalities in hepatic TB are nonspecific. Liver tests including aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT), total protein (TP) and albumin-

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[4] Bandyopadhyay S and Maity P. (2013) Hepatobiliary Tuberculosis. Journal of the association of physicians of india • june 2013 • VOL. 61

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globulin ratio, although found to be elevated in 30-80% of patients and are not diagnostic of hepatobiliary TB. A disproportionately increased serum alkaline phosphatase level is a consistent finding suggestive of an infiltrative hepatic process[13][14].

Approximately 75% of patients with hepatic TB are found to have abnormal chest x-rays demonstrating pulmonary TB. Calcification in the hepatic region on plain x-ray of the abdomen may occasionally be seen in local hepatic TB. In localized tuberculosis, ultrasound of the liver show hypoechoic lesions and complex masses. On CT scan, theses masses appear as non-enhancing, central, low-density lesions due to caseation necrosis with a slightly enhancing peripheral rim corresponding to surrounding granulation tissue. These appear similarly to necrotic tumor such as hepatocellular and metastatic carcinoma. CT-guided liver aspiration or biopsy can confirm the diagnosis. Laparoscopy can also be done to visualize lesions on the surface of the liver and obtaining a direct vision liver biopsy. Tuberculous lesions appear cheesy or chalky white irregular nodules of varying sizes. Percutaneous blind aspiration liver biopsy is useful in the diagnosis of the miliary form and tuberculous hepatitis. In the localized form of hepatic TB, ultrasound-, CT- or laparoscopic-guided liver biopsy yields a higher success rate. Visualization of the biliary tract is needed for patients with hepatobiliary TB presenting with obstructive jaundice. This can be accomplished by either endoscopic retrograde cholangiopancreatography (ERCP), percutaneous transhepatic cholangiography (PTC) or magnetic resonance cholangiopancreatography (MRCP). The site of obstruction was most commonly located at the porta hepatis and distal common bile duct. The bile ducts can appear beaded, with areas of dilatation and constriction[15].

Hepatobiliary tuberculosis is a treatable infection. The treatment regimen is similar to that of pulmonary tuberculosis. Initially, quadruple therapy (containing isoniazid, rifampicin, pyrazinamide and ethambutol) is recommended for at least two months and then the maintenance phase with dual therapy (isoniaizid and rifampicin) for atleast four months. Total duration of therapy can be extended to one year. For those patients with obstructive jaundice, biliary decompression should be done by stent placement during ERCP or percutaneous drainage. Surgery is attempted if there is dilated proximal common bile duct or hepatic ducts accessible for biliary-enteric anastomosis [16].

Pathology

The final diagnosis of hepatic TB, local as well as diffuse, rests on histopathologic evidence of caseating granuloma or demonstration of acid fast bacilli (AFB) on smear or culture of biopsy specimen. AFB stains are positive in about 60%. Polymerase chain reaction (PCR) assay for identification of *Mycobacterium tuberculosis* in liver biopsy specimens can also be done and are diagnostic in most patients with TB granulomas in the liver[17].

Irrespective of the mode of entry, the liver responds to tuberculous infection by granuloma formation. Granulomas are composed of epithelioid cells surrounded by lymphocytes, with or without Langhans' type multinucleated giant cells. Epithelioid granuloma formation in hepatic TB can be demonstrated in 80-100% of cases. In the miliary form, granulomas appear concentrated near the hepatic veins, whereas in focal form, the bacilli are found in the portal region[18] [6]. Both caseating and non-caseating granulomas are seen. Caseation, a hallmark finding of TB granulomas, is present in 33-100% of liver biopsy specimens from various series. With a finding of non-caseating granuloma in the liver biopsy specimen, a test AFB and/or culture of *Mycobacterium tuberculosis* would be required [19].

III. Methodology

Study Design

Retrospective review of all postmortem examinations performed in the Philippine General Hospital from 2003 up to 2012 was be done. All diagnosed cases of hepatobiliary tuberculosis will be included in the study. Based on chart review the following was reconstructed: chief complaints, cause of death, liver function test (AST, ALT, TB, DB, IB, ALP, Albumin and protime), imaging of the abdomen with special focus on the hepatobiliary system (Ultrasound, CT, MRI and MRCP or ERCP or PTHC if available) and histopathology/microbiology testing.

Liver Biopsy

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[19] ibid

Slides stained with hematoxylin-eosin and trichome will be retrieved and reviewed by a pathologist. Hepatobiliary tuberculosis is diagnosed based on the following definition: (1) presence of caseating granuloma formation or (2) presence of non-caseating ibidgranuloma formation with a positive smear for AFB or positive PCR.

Ethical Consideration and Budget

The protocol will be submitted for ethical review to the PGH Ethical Review Board. All records and information about the subjects will be kept strictly confidential. The Board will be granted access to the participants' records for purposes of verification of data. Authors and investigators will have data ownership and publication rights of the study. Funds (p1000) will be allocated for the paper and printer needed for completion of the manuscript. This will be shouldered by the investigators.

IV. Results

Out of the 755 autopsies performed from 2003 to 2012, 20 cases were found to have hepatobiliary tuberculosis. This represents 2% of the cases. The subjects ages ranged from 10 to 59 years old, with a mean age of 32 years old. The male to female ratio was 1.1:1 (1.1:1 in disseminated HBTB and 2:1 for localized HBTB). Length of stay in the hospital ranged from 0 to 13 days with a mean of 4.1 days. None of the subjects had prior history of liver disease. Two out of 20 cases had history of pulmonary tuberculosis, one received 6 months of treatment while the other was non-compliant to the treatment regimen. All cases were not known to have tuberculosis, and had not received treatment for their current condition. Most cases of hepatobiliary tuberculosis were the in the miliary form. This accounts for 85% of the cases. There was no granulomatous type of HBTB and there were 3 cases of localized HBTB (15%). Refer to table 1.

Most common chief complaint is decreased sensorium (35%) followed by dyspnea (25%), abdominal pain (10%), generalized body weakness (10%), abdominal enlargement (5%), fever (5%), syncope (5%) and Hip pain (5%). Most common causes of mortality were acute respiratory failure (30%) and TB meningitis (30%) followed by TB pericarditis (10%), secondary bacterial peritonitis (5%), GI bleeding (5%), cholangitis (5%), fatal arrhythmia (5%), heart failure (5%) and disseminated intravascular coagulopathy (5%). All of these deaths could be directly or indirectly be a consequence of tuberculosis infection. Only 1 case presented with hepatobiliary tuberculosis as an incidental finding. This was case 10, who passed away due to heart failure from metastatic pulmonary adenosqamous carcinoma. Refer to table 1 and appendix A.

Table 1: Demographics of Hepatobiliary Tuberculosis

Age	32 years old (10 to 59 years old)
Gender Disseminated HBTB Localized HBTB	1.1:1 (male to female ratio) 1.1:1 2:1
Length of Hospital Stay	4.1 days (0 to 13 days)
Co-morbities	Past PTB infection (1%)
Pre-morbid liver disease	None
Antemortem diagnosis of hepatobiliary tuberculosis	None
Tuberculosis Disseminated Granulomatous Localized	 17 cases (85%) 0 3 cases (15%)
Chief compliant Decreased sensorium Dyspnea Abdominal pain Generalized body weakness Abdominal enlargement Fever Syncope Hip Pain	 7 (35%) 5 (25%) 2 (10%) 2 (10%) 1 (5%) 1 (5%) 1 (5%) 1 (5%)
Cause of death TB meningitis Acute Respiratory Failure	 6 (30%) 6 (30%)

TB pericariditis	2 (10%)
Secondary bacterial peritonitis	1 (5%)
GI bleeding	
Cholangitis	1 (5%)
Fatal arrhythmia	1 (5%)
Heart Failure	1 (5%)
Disseminated intravascular	1 (5%)
coagulopathy	1 (5%)

Laboratories

Laboratory results of the subjects are presented in table 2. Liver function test on the average was deranged. AST and ALT were found to be elevated at a mean value of 138 and 51 respectively. In all 20 cases, AST had levels higher than ALT. ALP with a mean level of 303 IU/L, total bilirubin mean level of 285 ummol/L, direct bilirubin 106 ummol/L, indirect bilirubin 61 ummol/L and albumin 16 IU/L were also elevated. INR was normal at a mean of 1.39.

Table 2. Hepatic biochemical Results of Hepatobiliary Tuberculosis

	Normal values	Mean (range)
AST	15-41 IU/L	138 (22-647) IU/L
ALT	17-63 IU/L	51.6 (24-106) IU/L
ALP	32-91 IU/L	303 (118-572) IU/L
Total bilirubin	5.1-20.5 ummol/L	285 (19-619) ummol/L
Direct bilirubin	1.7-8.6 ummol/L	106 (3.53-170) ummol/L
Indirect bilirubin	3.4-11.9 ummol/L	61 (2.66-174) ummol/L
Albumin	35-48 IU/L	16 (11-22) IU/L
INR		1.39 (0.87-2.33)

Imaging

Only 4 cases had imaging studies available prior to demise. Uppper abdominal ultrasound findings were varied, case 1 presented with biliary ectasia secondary to an intraductal mass and hepatic nodules, splenomegaly with varices; case 6 presented with normal liver nad splenomegaly; case 10 presented with a 12x9.5cm solid mass and ascites and case 14 presented with perihepatic fluid and hepatomegaly. Refer to Table 3.

Table 3. Imaging findings of Hepatobiliary Tuberculosis

Case	Ultrasound
1	Biliary ectasia secondary to an intrahepatic duct mass: to consider Klatskin tumor; mild hepatomegaly with nodules; splenomegaly with varices; normal ultrasound of the gallbladder and pancreas There are enlarged vessels seen within the splenic hilum.
6	Mild splenomegaly; normal liver, pancreas, abdomainl aorta and para aortic areas and kidneys
10	12.3x9.5 cm hetergenous solid mass in the right liver lobe, minimal ascites. The rest of the findings were normal
14	Perihepatic fluid, an enlarged liver with smooth borders and normal parenchymal echopattern

Histopathologic Findings

Macroscopic findings of HBTB most commonly involves visualization of micronodules, with lesions measuring between 0.5-2cm in diameter. This is followed by grossly normal or enlarged liver. Adhesions on the surface capsule, macronodules (lesions measuring 1-3cm in diameter), mixed micro- and macronodules, enlarged perihepatic lymph nodes and calcifications were also described. Most lesions were disseminated (50%). Isolated right (17%), left (17%) and porta hepatis (17%) lesions were also described. Refer to Table 4.

Microscopic findings of HBTB universally presented with Chronic granulomatous inflammation with caseation necrosis and Langhan's type of Giant cells. Fibrosis was seen in seven cases. Refer to table 4.

Table 4. Histopathologic findings of Hepatobiliary Tuberculosis

Histopathologic Findings	Frequency

Macroscopic findings	
Hepatomegaly	5 / 20
Micronodules	8 / 20
Macronodules	1 / 20
Mixed (micro- and macronodular)	2 / 20
Adhesions on capsule	3 / 20
Enlarged perihepatic lymph nodes	2 / 20
Calfications	2 / 20
Normal	5 / 20
Microscopic	
Chornic granulomatous inflammation with caseation necrosis and Langhan's type of Giant cells	20 / 20
Fibrosis	7 / 20
Presence of AFB	2 / 2
Location	
Right lobe	2 (17%)
Left lobe	2 (17%)
Right + Left lobe	6 (50%)
Porta hepatis	2 (17%)

IV. DISCUSSION

Tuberculosis is a major public health problem in the Philippines and ranks ninth among the 22 high burden countries that account for 80% of the TB burden worldwide. The proportion of extra-pulmonary tuberculosis among all TB cases varies from country to country. In the Philippines, there were 4361 new extra-pulmonary cases diagnosed in 2014, which comprised 1% of the cases of tuberculosis identified in that year [CPG 2016]. Among the extrapulmonary cases, isolated hepatobiliary tuberculosis is found to be uncommon. In this study, 2% cases who underwent autopsy were found to have hepatobiliary tuberculosis.

The demographics of the subjects had a mean of 32 years old (10-59 years old), with a 1.1:1 male to female ratio. This is close to the study of Alvarez (2006) where hepatobiliary tuberculosis patients had a 2:1 male preponderance with majority within 11-50 years and with peak incidence in the second decade in both sexes[20]. This coincides with the age incidence of pulmonary tuberculosis among Filipinos. All subjects had no prior history of liver diseases. And only 2 had past history of pulmonary tuberculosis. One case had received adequate treatment of 6 months and subsequently had a histopathologic finding of healed granuloma in the liver. The second case had inadequate treatment, which could be a factor in the development of disseminated tuberculosis. None of the cases were diagnosed with tuberculosis prior to demise and only one case had received anti-tuberculosis medication during the course of the hospital stay. Delayed recognition and management are factors that may have contributed to the demise of the subjects.

The liver can be involved during the tuberculosis process in various ways. Miliary form, which is tuberculosis in the liver that is part of a generalized infection, is the most common type. It is said to occur in 50-80% of all patients dying from pulmonary tuberculosis. This was found true in this study wherein 85% of HBTB were found to have concomitant extrahepatic and a pulmonary source. This result could be secondary to sampling bias given that severe cases encountered in an autopsy series would logically be of the miliary type. This form arises when the organism reaches the hepatobiliary tract by the hematogenous route, from a tuberculous infection of the lungs via the hepatic artery[21]. Localized hepatobiliary tuberculosis involve solitary or multiple nodules, tuberculoma and tuberculous hepatitis; or bile duct involvement causing obstructive jaundice either by enlarged nodes surrounding the bile ducts or acute tuberculous processes in the ductal epithelium[22]. It can develop through enlargement and subsequent confluence of the miliary foci or tubercles as well as through nodular development of tuberculous foci in the tertiary stage[23]. This form is rare, with a frequency of 0.8-1.2% in international reports[24][25]. This study; however, showed a much higher frequency of localized HBTB at 15%. This was also described in other reports wherein hepatobiliary TB was seen more commonly in the

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Philippines and among Filipino patients abroad and there is no explanation for this kind of occurrence but it has been suggested that Filipinos may have racial vulnerability to the tubercle bacilli[26].

The chief complaints of the cases were mostly unrelated to the gastrointestinal tract. Most common were decreased sensorium (35%) and dyspnea (25%) and these correlated with the top 2 causes of mortality which are TB meningitis (30%) and acute respiratory failure (30%) respectively. The rationale behind this is that the clinical manifestations of the disseminated type of HBTB are those of the primary extra-hepatic disease. Disseminated form of HBTB was the most frequently encountered type in this study and hepatic involvement in such instances are usually asymptomatic[27]. Symptoms of hip pain (5%) was also explained in light of the diagnosis of TB osteomyelitis. Syncope (5%) developed due to fatal arrhythmia from Takayasu arteritis. Localized HBTB was just an incidental finding. The rest of the reason for admission were as follows: abdominal pain (10%), generalized body weakness (10%), abdominal enlargement (5%) and fever (5%). These are consistent with symptoms of HBTB. Past studies have reported fever, anorexia, weight loss, abdominal pain, jaundice, nausea or vomiting, abdominal distension, and ascites [28][29]. Of these symptoms, right upper quadrant or non-specific abdominal pain were the most common symptom present in 65-87% of patients [30]. Jaundice is an uncommon presentation, being present in 20-35% of patients. The presence of jaundice suggests biliary involvement, and the biochemical profile may simulate extrahepatic biliary obstruction [31].

Baseline laboratories of the subjects were found to be abnormal. AST and ALT were elevated. Though literature have noted this abnormality in both localized and disseminated HBTB. In localized HBTB, elevation of liver enzymes are usually encountered in tuberculosis that directly involve the biliary epithelium, rupture of a tuberculous granuloma into the bile ducts or due to biliary stasis from hepatic nodes compression of the bile ducts[32]. In this subset of cases, 91-94% of subjects have elevated transaminases[33]. No definite range have been not established yet. Disseminated tuberculosis involving the liver may also have elevation of transaminases. This was explained by the release of granular enzymes and oxidants which participate in local inflammation and eventually activate an inflammatory casecade reaction that lead to other organ dysfunction as reflected by an increase in the AST and ALT. In one study performed in China, AST ALT and albumin were used as prognostic factors and were used as independent predictors of ARDS development in patients with military tuberculosis[34]. ALP was also found to be elevated in all cases of hepatobiliary tuberculosis. This coincides with reports in the literature that states that this, alongside y-glutamyl transpeptidase levels, is the most common specific hepatic biochemical abnormality associated with HBTB. This typically ranges from 200-750 IU/L and can be seen in jaundiced as well as non-jaundiced patients. ALP was found to be elevated in more than 75% and 92% of patients in the Philippines and South African series[35]. ALP are present on the canalicular and luminal domain of the bile duct epithelium and levels rise as a result of increased synthesis and consequent release into the circulation due to the infiltrative process of hepatobiliary infections[36] [37]. Jaundice, in literature review, was noted occur in 20-35% of cases[38] [39]. If present, this was attributed to direct destruction of liver parenchyma or biliary tract obstruction from enlarged tuberculous lymph nodes are also known cases. Direct bilirubinemia and jaundice was noted to occur in 70% of the cases, a much higher rate stated in the reports. Additional factors such as sepsis and ischemia may have contributed to this occurrence. Albumin was depressed in all 20 cases in the study. This was supported by literature that reports hypoalbuminaemia and hyperglobulinaemia to be present in approximately 80% of patients with hepatobiliary TB. Localized and diffuse inflammation that is consequence of tuberculosis infection suppresses the synthesis of albumin in the liver. Normal INR connotes synthetic function of the liver was not affected.

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Multiple imaging modalities can be used to diagnose hepatobiliary tuberculoisis. Liver calcifications on abdominal x-ray described as multiple chalky or powdery calcifications in the liver, nodes or along the course of the common bile duct are highly suggestive of hepatobiliary tuberculosis[40]. One study reported this occurrence in approximately 50% of patients[41]. This; however, was not performed in our patient. Another imaging commonly performed in hepatobiliary tuberculosis is abdominal ultrasound. Abnormalities in the latter was found in a median proportion of 76% (range: 6-100%). Evident from the results of this study, ultrasonographic findings of HBTB are varied. This is so because the microorganism affects the liver in different ways. Liver involvement of tuberculosis can be classified as micronodular or macronodular. Micronodular HBTB refers to military tuberculosis wherein lesions measure 0.5-2cm in diameter. The macronodular form may present either as multiple 1 - 3 cm lesions or as a large tumor-like mass. Mixed type of hepatic TB have also been described, which demonstrates both micronodular and macronodular features. The micronodular form of hepatic TB is more common and is thought to result from hematogenous dissemination of TB bacilli. If these lesions are below the resolution of the ultrasound, the only imaging finding in micronodular hepatic TB may be hepatomegaly[42]. This may explain the normal findings and presence of hepatomegaly in case 10 and 14 respectively. US may also demonstrate lesions as tiny hypoechoic lesions with a "bright liver pattern." The macronodular form of hepatic TB is less frequent and is probably secondary to conglomeration of miliary granulomas. Macronodules on US appear as hypoechoic lesions or complex masses[43] as evident in case 6. Dilated intrahepatic ducts in obstructive jaundice can be demonstrated by ultrasound as evident in case 1. CT scan and MRI imaging are also commonly used. Though may be more informative, both exams may still be insufficient to confidently diagnose hepatobiliary tuberculosis and histopathologic diagnosis should always be attempted. Both exams were not performed in the cases.

Macroscopic findings of HBTB most commonly involved visualization of micronodules, with lesions measuring between 0.5-2cm in diameter. This supports the demographics of disseminated tuberculosis as the predominant form of HBTB found in this case. Other findings were as follows; grossly normal or enlarged liver, adhesions on the surface capsule, macronodules (lesions measuring 1-3cm in diameter), mixed micro- and macronodules, enlarged perihepatic lymph nodes and calcifications were also described. All microscopic findings revealed chronic granulomatous inflammation with caseation necrosis and Langhan's type of Giant cells, which is diagnostic for HBTB. Histologic evidence of non-caseating granuloma formation will require positive smear for AFB to increase specificity. This was done in 2 cases, both were positive. Noteworthy is the presence of hyalinized areas suggestive of fibrosis most marked in case 10. This was probably a sequelae of previous treatment with antituberculosis medications. Histopathologic findings revealed predominantly fibrotic lesions with few small Langhan's type giant cell. This was signed out as healed granulomata. This connotes that with treatment and resolution of the infection, fibrosis may be an eventual and permanent phase.

IV. Conclusion

Presenting symptoms of HBTB may be unrelated to the gastrointestinal tract. Liver function test derangement are common; however are nondiagnostic. Ultrasound findings may range from normal to a complex mass causing biliary ectasia. Histopathologic findings of chronic granulomatous inflammation with caseation necrosis and Langhan's type of Giant cells are diagnostic; however acquisition of tissue sample is problematic. Therefore, diagnoses and management require a high index of suspicion.

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I. Appendix A

	Age/ Sex	Hospital stay	Co-morbidities	Chief Complaint	Type of HBTB	Known TB	Clinical Diagnosis	Cause of Death
1	19/ M	4 days	None	Dyspnea	Localized	Yes	A. Portal hypertension secondary to tuberculosis of the porta hepatis with extrahepatic biliary obstruction; multiple hepatic abscesses; hepatomegaly; splenomegaly; jaundice; ascites; grade II bipedal edema B. Severe pulmonary edema with pneumonia bilateral	Acute respiratory failure
2	10/ M	2 days	None	Abdominal enlargement	Disseminated	No	A. Disseminated tuberculosis (lungs, liver, thoracoabdominal wall, diaphragm, omentum, lymp nodes, pancrease, adrenal gland, left anterior chest, left arm and right gluteal area B. Congestive splenomegaly C. Stress gastritis D. Anthracosis, both lungs, mild stunting and severe wasting	Acute Repiratory Failure
3	22/ M	8 days	None	Abdominal pain	Disseminated	No	A. Disseminated tubercutlosis (lungs, pleural effusion, gastrointestinal tract, liver, gallbladder, spleen, mesentery with small and medium vessel vasculitis, kidneys, lymph nodes B. Cystitis C. Ascariasis	Hypovoelmic shock secondary to GI bleeding secondary to Agastrointestinal and mesenteric tuberculous vasculitis
4	42/ M	1 day	None	Decreased sensorium	Disseminated	No	A. Bronchopneumonia, bilateral B. Disseminated tuberculosis (lymphocytic meningoencephalitis, lungs, lymphoadenitis, liver and spleen)	TB meningitis
5	15/ M	5 days	None	Decreased sensorium	Disseminated	No	A. Disseminated tuberculosis (meningitis with cerebral edema; gastrointestinal tuberculosis; tuberculous hepatitis; lymph nodes) B. Bronchopneumonia with pulmonary edema C. Hypoxic changes, intraventricular septum and left ventricular wall	Tuberculous meningitis
6	24/F	8 days	None	Generalized body weakness (cough, neck mass, anorexia, weight loss, fever, decreased sensorium)	Disseminated	No	A. Disseminated kochs infection (pericardium with pericardial effusion; lungs; liver; spleen; left kidney; lymph nodes) B. Mucosal hemorrhages, ileum C. Immunocompromised state	Cardiac tamponade secondary to tuberculous pericarditis
7	30/ M	3 days	None	Decreased sensorium (scrotal pain, swelling, fever, headache)	Disseminated	No	A. Disseminated tuberculosis (meningoencephalitis, lungs, liver, spleen, pancrease, kdineys, eipdidymo-orchitis, prostatitis	Tuberculous meningitis
8	67/ M	0 days	None	Decreased sensorium (abdominal pain, loose watery stool, fever, jaundice, edema, behavioral changes)	Disseminated	No	A. Disseminated tuberculosis (liver, lungs, spleen, kidneys, pancreas, adrenals, thyroid, lymph nodes B. Cryptosporidiosis, pancreas C. Oral hairy leukoplakia with candidiasis D. Diffuse alveolar damange bilateral E. Stress gastritis F. Atherosclerosis: aorta severe and left circumflex artery with 75% occlusion	Cholangitis secondary to HBTB

9	14/F	0 days	None	Syncope (Chest pain)	Localized	No	A. Non specific acute necrotizing aortitis involving the ascending aorta, coronary artery ostia and proximal coronoary arterieis and inter-atrial septum B. Pulmonary congestion and eema with focal hemorrhage, bilateral C. Tuberculous nodules, liver D. Atherosclerosis, mild, aorta E. Epicardial petechiae and hemorrhage into the thymus and mediastinal soft tissues, probably secondary to resuscitative measures	Fatal arrhythmia secondary to Takayasu arteritis
10	61/ M	0 days	s/p PTB treatmen t	Dyspnea (cough, fever, hemoptysis,	Localized	Yes	A. Pulmnoary adenosquamous carcinoma, right lower lobe, with metastasis to heart, left lung, soft tissues, right and left adrenal glands, left kidney, pancreas and lymph nodes B. Pleural adehsions left lung C. Healed granulomata, liver	Heart failure secondary to cardiac metastasis from pulmonary adenosquamou s carcinoma
11	41/F	0 days	None	Abdominal pain (loose watery stool, melena, weight loss)	Disseminated	No	A. Disseminated tuberculosis (ileocecum, ruptured; liver; left ovary; diaphragm) B. Pleural effusion C. Erosive gastritis D. Atherosclerosis mild E. Hyperplastic nodule, right thyroid lobe	Secondary bacterial peritonitis secondary to ruptured GITB
12	50/ M	12 days	None	Decreased sensorium	Disseminated		A. Lobar pneumonia right B. Atherosclerosis moderate C. Disseminated tuberculosis (lungs, pericardium, liver, gallbladder, spleen) D. Intestinal ascariasis	Acute respiratory failure secondary to peumonia
13	19/F	12 days	None	Fever	Disseminated	No	A. Disseminated tuberculosis (meninges, right lung, bilateral kidneys, ileocecum and liver) B. Acute hemorrhagic gastritis	TB meningitis
14	59/ M	13 days	s/p PTB treatmen t	Decreased sensorium	Disseminated	No	A. Disseminated tuberculosis (lungs, liver, spleen, pericardium) B. Anemia of chronic disease	TB pericarditis
15	14/ M	0 days	None	Generalized weakness	Disseminated	No	A. Disseminated tuberculosis (meningitis, pulmonary, liver, lymph nodes, bone marrow, pituitary gland, spleen, colon, right ear)	TB meningitis
16	27/F	1 day	None	Dyspnea	Disseminated	No	A. Disseminated tuberculosis (lungs, liver, spleen, kidneys, thyroid, pancreas, lymph nodes) B. Left ventricular lypertrophy	Acute respiratory failure
17	31/F	9 days	None	Decreased sensorium	Disseminated	No	A. Disseminated tuberculosis (cerebral cortex, cerebellum, meninges, lungs, lymph nodes, liver, gallbladder, spleen, kidneys, ureter, urinary bladder, terminal ileum, cecum, mesentery, uterus and fallopian tubes) B. Reactive splenomegaly C. Chronic choelcystitis with cholecystolithiasis D. Decubitus ulcer E. Malnutrition with anemia, moderate to severe	TB meningitis
18	16/F	2 days	None	Dyspnea	Disseminated	No	A. Acute respiratory distress syndrome secondary to severe bronchopneumonia, bilateral B. Disseminated tuberculosis (pulmonary, liver, spleen)	Acute respiratory failure
19	43/F	2 days	None	Hip pain	Disseminated	No	A. Disseminated tuberculosis (lungs, bone, pericardium, liver, spleen, lymph nodes, adrenals)	DIC 2o Disseminated tuberculosis

							B. Disseminated intravascular coagulopathy C. Colloid nodules thyroid D. Endometriotic cyst left ovary	
20	35/F	0 days	None	Dyspnea	Disseminated	No	A. Acute respiratory distress syndrome B. Disseminated tuberculosis (lungs, liver, pancreas, spleen, kidneys, adrenals) C. Hemoperitoneum D. Subcapsular hematoma liver E. Papillary microcarcinoma, thyroid, right lobe	Acute respiratory failure

II. Appendix B

Patient	AST (IU/L)	ALT (IU/L)	ALP (IU/L)	TB (ummol/L)	DB	IB	Albumin (IU/L)	INR
1	152	72	426	333			17	
3	105	43	214	19	7.2	11.8	14	0.87
5								0.96
6	99	62	123				11	
7								1
8	75	50	325	506	332	174	13	
10	19	24	118	6.19	3.53	2.66	19	
11								
13							22	
14	75	39	467	284	170	114	15	2.12
16	120	58	512	207	149	58		1.34
17	22	29					22	1.11
18	647	106						
19	74	33	179	33	27	6.8	11	2.33

III. Appendix C

Patient	Macroscopic view	Microscopic
1	The liver weighs 2300grams (1500-1800). The inferior edge is sharp. The capsule is tan white, smooth, glistening with note of fibronous adhesions on its superior surface. The surface is tan brown with several round, cream yellow, raised nodular and cystic leisons with sizes ranging form 0.2 to 2.8cm. Cut sections show a firm tan brown parenchyma with several discrete and some confluent cystic and nodular areas filled with cream yellow purulent material concentrated mostly around the porta hepatis or hilum of the liver. Several hepatic lymph nodes (0.5-1.5cm are noted)	Sections from the liver reveal lobular disarray with abundant periportal and bridging fibrosis. There are multiple lymphocytic infiltrates within the portal triads as well as the liver parenchyma. There is also note of numerous pink, acellular necrotic areas surrounded by numerous giant cells. The nuclei of the giant cells are distributed about the periphery. Section from the hepatobiliary tree reaveal bile duct and vessels surrounded by fibrosis and necrosis. Sections from the perihepatic lymph nodes reveal areas of necrosis surrounded by giant cells and numerous lymphocytic infiltrates that are arranged in follicles, but some of the follicles are replaced by pink areas of caseation of Langhan's type giant cells. Chornic granulomatous inflammation with caseation necrosis and Langhan's type of Giant cells consistent with TB
2	The liver is markedly enlarged weighing 1050grams (852 grams). The capsule is red-brown with multiple yellow-white nodules of varying sizes on all surfaces. There is a 9x7.5x2cm soft tan brown well circumscribed mass found arising from the posterior surface of the right lobe. The liver is generally firm and its edges are blunted. Serial cut sections show a red-brown soft to firm parenchyma with multiple yellow-white firm coalescent nodules of varying sizes, interspersed with firm areas of fibrosis. There are two ill defined nodules composed of green-black coarse granular material measuring 2x1.1x1.1cm and 2x1.9x1.4cm respectively and located at the central portion of the right lobe and inferior portion of the left lobe respectively.	Microscopic sections shows granuloma formation with central caseation necrosis. There are also large areas of fibrosis with intervening areas of normal liver parenchyma. Focal areas of lymphocytic infiltration was also noted. Chronic granulomatous inflammation with caseation necrosis and fibrosis consistent with tuberculous infection, liver
3	Gross: no apparent surface nodularities. Cut section showed a 1 cm yellow nodule dilating one of the intrahepatic ducts. Rest of the liver had homogenous brown parenchyma	Chronic granulomatous inflammation with caseation necrosis and Langhan's type giant cells
4	Hepatic surface was smooth, brown, glistening. Cut sections show a reddish brown cut surface with focal congested areas. No masses seen.	Interspersed in the liver parenchyma were multiple foci of lymphoplasmacytic infiltrates with sparse Langhans type giant cells and occasional central necrosis.

5	Capsule is tan to brown and glistening. On cut sections, noted multiple cream white ill defined nodules through the parenchyma in the background of dark brown homogenous cut surface	Chronic granulomatous inflammation with caseation necrosis and Langhans type giant cells
6	Edges are round, capsule is tan white, smooth, glistening and free from adhesions. The surface is tan brown and smooth. Cut sections show a homogenous granular parenchyma.	Chronic granulomatous inflammation with caseation necrosis and Langhans type giant cells
7	Inferior edge is sharp, the capsule is tan white, smooth, glistening and free from adhesions. Surface is tan brown and smoth. Cut sections show a homogenous, red brown parenchyma	Focal, chronic granulomatous inflammation with caseastion necrosis and Langhan's type giant cells
8	Edges are round. Capsule is tan, white, glistening and free from adhesions. The surface is tan brown, smooth, and there were multiple minute light yellow nodules. Cut sections show a homogenous granular parenchyma with multiple minute yellow nodules. There were note of enlarged lymph nodes in the porta hepatis	Intact liver sinusoids. There is congestion around the central vein of each lobule. Few lymphocytes and neutrophils surround the portal triad and piecemeal necrosis were noted; Diffuse, chronic granulomatous inflammation with caseastion necrosis and Langhan's type giant cells
9	Weight is 1025grams (800-930grams). The Edges are round. The capsule is grey, smooth, glistening and free from adhesions. The surface is smooth and red brown with multiple yellow subcapsular nodules, 0.5 to 0.8cm in diameter, on the anterior and posterior surfaces of the liver. Cut sections show homogenous red brown parenchyma interspersed with bile duct lumina and blood vessels. The nodules were cream-white friable to soft cut surfaces.	Hepatic nodules are foci of chronic granulomatous inflammation characterized by central caseation type of necrosis, peripheral fibrosis and presence of few Langhans type giant cells
10	Weight is 1870 (1500-1800). There are areas with several yellow firm masses on its outer surface measuring 1 to 4cm. Sections of the liver shows a smooth, homogenous red brown surface. It shows a yellow, gritty cut surface which seem to have a central area of calcification.	Microsection sofhte liver show foci of caseation necrosis with predominantly hyalinized areas suggestive of fibrosis and few, small, Langhan's type giant cells (Healed granulomata, liver)
11	Liver weighs 1640 grams (1500-1800) The capsule is thin, smooth and glistening. A 1x1x0.5cm cream white soft mass is noted at the anterior surface of the right lobe of the liver. Cut section of the masses show cream white cheesy surface. Rest of the liver showed cream-brown, firm parenchyma.	Chronic granulomatous inflammation with caseation necrosis and Langhan's giant cells consistent with tuberculosis
12	Liver weighs 1200grams and is normal in size and shape. Ther inferior edge is sharp. The capsule is thin and smooth with no adhesions. The surface is homogenously red brown parenchyma separated by connective tissue strands.	Diffuse chronic granulomatous inflammation with caseation necrosis and Langhan's giant cells; intracellular bile stasis
13	Liver weighs 1640grams. The capsule is thin, smooth, and glistening. There are multiple cream white cheesy white millet seed like nodularities at the porta hepatis. Posterior view shows diffuse fibrinous adhesions at the external surface of the left lobe. Serial cut sections showed cream-brown firm parenchyma.	Diffuse chronic granulomatous inflammation with caseation necrosis and Langhans type giant cells at the porta hepatis
14	Liver weighs 1200grams and is normal in size and shape. The inferior edge is sharp. The capsule is thin and smooth with no adhesions. The surface is homogenously red-brown in color. The liver is homogenously firm on palpation. Cut surfaces showed a red brown parenchyma separated by connective tissue strands.	Diffuse chronic granulomatous inflammation with caseation necrosis and Langhans type giant cells with occasional hyalinized tubercles, destruction of the liver lobular architecture and bile stasis.
15	Liver is 800grams (normal). There are multiple cream yellow, firm areas involving the anterior segments of the liver more prominent on the left.	Hepatic parenchyma is interrupted by multiple caseating granulomas with langhans type gianct cells and significant portion of the left lobe is replaced by caseating lesion
16		Histologic section show focal area of epitheloid cell proliferation and scanty caseation necrosis and few multinucleated giant cells mostly in the portal tracts seen in the background of hepatic steatosis; fite faraco stain was positive for acid fast bacilli
17	The liver weighs 1500grams. There are multiple cream tan, firm lesions ranging from 0.5 – 2.5cm scattered all over the anterior and posterior surfaces. Cut section shows foci of well distributed parenchymal lesions with fibrocalcific surface and caseous material.	Microscopic sections show well developed granuloma formation with Langhan's type giant cells in the liver parenchyma. There are fibrosis, calcifications and infiltration of the chronic inflammatory cells interspersed in between areas of normal hepatic parenchyma and in the portal triads

18	The liver weigh 1600grams. The surface is maroon red with areas of lividity at the posterior surface. Cut section of the liver show firm homogenous maroon to brown parenchyma.	Microscopic findings show liver congestion. There are also Langhangs type giant cells surrounded by inflammatory cells.
19	The liver weigh 1550grams. The surface is yellow brown and smooth with multiple cream yellow circular discolorations measuring 0.3cm in average diameter. Cut section of the liver shows a yellow brown parenchyma with multiple cream yellow nodules measuring 0.5cm in average diameter.	Microscopic findings show granulomatous inflammation with caseation necrosis; Fite faraco stain positive for acid fast bacilli
20	The liver weigh 2050 grams (1000-1500). The capsule is smooth and thin. Cut section showed maroon, firm parenchyma.	Numerous foci of chronic granulomatous inflammation with severeal Langhan's type giant cells and caseation necrosis